

Aortic Valve Involvement in Behçet's Disease. A Clinical Study of 9 Patients

Choong Won Lee, M.D., Jisoo Lee, M.D.*, Won Ki Lee, M.D.*,
Chan Hee Lee, M.D.*, Chang Hee Suh, M.D.*, Chang Ho Song, M.D.*,
Yong Beom Park, M.D.*, Soo Kon Lee, M.D, Ph.D.*
and Yong Soon Won, M.D, Ph.D.[†]

Division of Rheumatology, Department of Internal Medicine, Wallace Memorial Baptist Hospital, Busan, Korea; Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea; Department of Thoracic Cardiovascular Surgery, St. Mary's Hospital, Catholic University, Taejeon[†], Korea.*

Objectives : To assess the clinical features, pathologic findings, postoperative results and the effects of immunosuppressive therapy in patients with Behçet's disease (BD).

Methods : We reviewed the postoperative course of the 9 BD patients who underwent a total of 17 aortic valve replacement procedures with prosthetic valves.

Results : Histological examination of the aortic valve commonly revealed diffuse myxoid degeneration (75 percent). Of 17 valve replacement surgeries, 13 surgeries resulted in complications, such as detachment of the prosthetic valve with perivalvular leakage and dehiscence of the sternotomy wound, within an average of 5 months (range from 1 month to 14 months). The rate of prosthetic valve detachment was 76 percent (13 of 17 surgeries). Four of the 9 patients (44 percent) who underwent aortic valve replacement procedures died of heart failure or infection associated with the detachment of the prosthetic valve, and perivalvular leakage within an average of 9 months. Aortic insufficiency associated with dehiscence of the prosthetic valve developed in 11 of 12 surgical cases (92 percent) with a mechanical valve and 2 of 5 surgical cases (40 percent) with tissue valves. Thirteen of 15 surgeries (87 percent) which were not given postoperative immunosuppressive therapy developed complications, while none of 2 surgeries that used postoperative immunosuppressive therapy with prednisolone (1 mg/kg/day) and azathioprine (100 mg/day) had these complications.

Conclusion : The rates of prosthetic valve detachment in BD involving aortic valve were higher than those of other diseases. Aortic valve involvement was also one of the poor prognostic factors in BD. Intensive postoperative immunosuppressive therapy and surgical methods may be important factors for postoperative results.

Key Words : Behçet's disease, aortic insufficiency, immunosuppressive therapy

INTRODUCTION

Behçet's disease (BD) is an inflammatory condition of multiple organ systems in which recurrent oral and genital

ulcers are the most typical signs¹. BD associated with large vascular lesions is called vasculo-BD, the major manifestations of which are aneurysm formation, arterial occlusion and venous occlusion. Reported cardiovascular involvement includes pericarditis, myocarditis, conduction system disturbances, acute myocardial infarction and cardiomyopathy²⁻⁴. Aortic valvular involvement in BD, however, has rarely been reported. In 1980, Rae et al.⁵ first reported a case of BD with aortic insufficiency.

Address reprint requests to : Choong Won Lee, M.D.,
Division of Rheumatology, Department of Internal
Medicine, Wallace Memorial Baptist Hospital, Gumjung-
Gu P.O Box 100 Namsan-Dong Gumjung-Gu, Busan,
Korea. 609-340

Eight cases that have been reported in English literature revealed that most patients needed valve replacement and resulted in serious complications such as dehiscence of the prosthetic valve, perivalvular leakage, false aneurysm at the cannulation site, dehiscence of the sternotomy site and death⁵⁻¹¹. Modified surgical technique, such as valved conduit procedure, recently has suggested decreasing the postoperative complications^{12, 13}. It is suggested that new surgical and medical therapies are needed to reduce the postoperative complications and mortality rates.

So, we have identified aortic valvular insufficiency in 9 patients with BD who underwent a total of 17 valve replacements. Clinical features, pathologic findings, postoperative complications, surgical methods and immunosuppressive therapy were compiled.

PATIENTS AND METHODS

1. Patients

We reviewed the medical records of the 10 Korean patients with BD who received aortic valve replacement because of severe aortic insufficiency. Three of the 10 patients underwent surgery at Seoul National University Hospital from 1986 to 1988. Seven of the 10 patients underwent surgery at Yonsei University Medical Center from 1990 to 1997. One of these 10 patients who had rheumatic fever in the past history, however, was excluded from the study.

None of the 9 patients had rheumatic fever, bacterial endocarditis or congenital heart disease before entering the study. All sera were negative for antinuclear antibodies, rheumatoid factor and VDRL. None showed the characteristic stenosis of the aortic arch and its branches as seen in Takayasu's arteritis. None showed vegetations

or calcifications on the aortic valve in echocardiography. None of the patients exhibited characteristic findings of rheumatic valvular disease, which includes thickening, deformity and shortening of multiple valves.

None of the patients were older than 42 years of age. Seven of the 9 patients developed aortic insufficiency during the follow-up for BD; two patients were diagnosed with BD after developing aortic insufficiency.

2. Surgical methods and follow-up (Table 2)

These 9 patients underwent a total of 17 aortic valve surgeries. The operation time was dyspnea associated with heart failure or moderate to severe aortic regurgitation on echocardiography. The surgical procedures of aortic valve replacement were with the following prosthetic valves: St. Jude, Carbo Medics (S-J, C-M)(Nos. 2a, 2b, 3a, 3b, 3c, 4, 6a, 8b, 9a, 9b, 9c), tissue valves: Inoescu Shiley (IS) (Nos. 7, 8a) and autografts with pulmonic valve or pericardium (Nos. 1, 5, 6b). We followed up to see postoperative complications with transthoracic or transesophageal echocardiography at 2 to 3 months intervals after surgery (range from 2 months to 3 years and 10 months).

3. Immunosuppressive therapy

After surgery, immunosuppressive therapy with prednisolone (1 mg/kg/day) and azathioprine (100 mg/day) was given in 2 patients (Nos. 5, 6b) who had no evidence of bacterial or fungal infection on the frozen section of valve or endocardium, or during tissue culture. Prednisolone was tapered after 2 months and azathioprine was continued at the same dose for an average of 19 months.

4. Statistical analysis

The association with postoperative complications between each surgical method and immunosuppressive

Table 1. Clinical features of Behçet's disease in 9 patients with aortic valve involvement.

Patient No.	Sex	Age (yrs)	Duration of disease	Dyspnea Onset	Aphthous stomatitis	Ocular lesions	Symptoms of BD		
							Skin lesions	Genital ulcers	Other symptoms
1	M	32	11 yr	Acute	+	+	+	+	Arthritis
2	F	39	12 yr	Acute	+		+	+	
3	M	28	2 mo	Acute	+		+		Vasculitis
4	F	22	2 yr	Insidious	+	+	+		Arterial occlusion
5	M	42	2 yr	Insidious	+		+		Arthritis, Vasculitis
6	M	36	3 yr	Acute	+		+		Vasculitis
7	F	32	2 mo	Acute	+		+		Arthritis, Vasculitis
8	M	36	1 yr	Acute	+		+	+	Arthritis, Thrombophlebitis
9	M	34		Acute	+		+	+	Aortitis

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therapy were analyzed using Fisher's exact test. The level of significance was set at $p < 0.05$.

RESULTS

The mean age of 5 men and 4 women patients when entering into the study was 33 ± 6 years (range from 22 to 42 years of age).

Five patients (Nos. 1, 2, 4, 8, 9) had three or more major symptoms (aphthous stomatitis, genital ulcers, skin lesions and/or ocular lesions). Two patients (Nos. 5, 7) had two major symptoms (aphthous stomatitis and skin lesion) and two minor symptoms (arthritis and vasculitis). Two patients (Nos. 3, 6) had two major (aphthous stomatitis and skin lesions) and one minor symptom (vasculitis) (Table 1). According to Shimizu's classification (14), we had one (Nos. 1) complete BD, 4 (Nos. 2, 4, 8, 9) incomplete BD and 4 (Nos. 3, 5, 6, 7) suspected BD. Three patients (Nos. 7, 8, 9) were previously reported as cases¹⁵. The major manifestations of BD were aphthous stomatitis and skin lesions (100 percent), genital ulcers (44 percent) and ocular lesions (22 percent) (Table 1).

Seven patients (78 percent) acutely developed dyspnea on exertion. Aortic insufficiency was developed late in the

course of BD (average of 3 years and 11 months; range from 2 months to 12 years) (Table 1).

Valve involvement consisted of 5 isolate aortic insufficiency (56 percent) and 4 combined aortic and mitral insufficiency (44 percent). Two patients (Nos. 1, 2) had concomitant complete atrioventricular block (Table 2).

The macroscopic findings of the aortic valve and aortic wall included central perforation of the cusp with aneurysm of the Valsalva sinus in 4 patients (44 percent), annular dilatation in 3 patients (33 percent) and fused valves with or without myxoid change in 2 patients. The microscopic pathologic features of the aortic valve among 8 valves that were available after surgery included diffuse myxoid change and fibrin exudation in 6 cases (75 percent), focal nodular necrosis in 1 case and fibrous thickening with mucin deposit in 1 case. The microscopic findings of the aortic wall among 6 aortic walls that were available after surgery included destruction or cystic degeneration of the tunica media in 3 cases (50 percent), fibrotic change in 2 cases (30 percent), active inflammatory cell infiltration on media, adventitia and peri-vasa vasorum in 1 case and marked mucopolysaccharide deposition in 1 case (Table 3).

Nine patients underwent a total 17 valve replacement surgeries and 13 surgeries resulted in complications

Table 2. The characteristics of Behçet's disease in 9 patients with aortic valve involvement.

Patient No.	Cardiovascular signs	Surgical procedure (AV)	Complications after operation	Elapse time to complication	Length of follow-up	Immunosuppressive therapy
1	AR, complete AVB	Ross op.	DPV, Death	1 mo.	2 mo.	None
2a	AR, complete AVB	AVR with CM	DPV	7 mo.		None
b	AR	AVR with CM	DPV, Death	7 mo.	14 mo.	None
3a	AR	AVR with SJ	DPV	14 mo.		None
b	AR	AVR with CM	DPV	4 mo.		None
c	AR	AVR with SJ	DPV, Death	1 mo.	19 mo.	None
4	AR, MR	Bental op. with SJ	None		46 mo.	None
5	AR, MR	CR with Pericadium	None		20 mo.	PDS+AZA
6a	AR	AVR with CM	DPV, DTS	4 mo.		None
b	AR	Ross op.	None		18 mo.	PDS+AZA
7	AR	AVR with IS	None		2 6 mo.	None
8a	AR, MR	AVR with IS	DPV	2 mo.		None
b	AR	AVR with SJ	DPV, Death	5 mo.	9 mo.	None
9a	AR, MR	AVR with SJ	DPV	6 mo.		None
b	AR	AVR with SJ	DPV	4 mo.		None
c	AR	AVR with SJ	DPV	4 mo.		None
d	AR	Patch with SJ	DPV	1 mo.	19 mo.	None

AV, aortic valve; AVB, arterioventricular block; AVR, aortic valve replacement; AR, aortic regurgitation; MR, mitral regurgitation; TR, tricuspid regurgitation; CR, cuspid replacement; CM, Carbo Medic valve; SJ, St. Jude valve; IS, Ionescu Shiley bovine valve; DPV, detachment of prosthetic valve; DTS, dehiscence of thoracotomy site; PDS, prednisolone; AZA, azathioprine; op., operation; mo, month

Table 3. Pathologic findings of the aortic valves and thoracic aorta in surgical patients with aortic regurgitation caused by Behçet's disease.

Macroscopic Finding	Patient No.								
	1	2	3	4	5	6	7	8	9
Macroscopic Finding									
Fenestration of cusp	+	+			+			+	
Valsalva sinus aneurysm									
Annulus dilatation				+			+		+
Fused cusp			+			+			
Microscopic finding of AV									
Diffused myxoid change				+	+	+	+	+	+
Focal nodular necrosis		+							
Fibrosis thickening	+								
Microscopic finding of AW									
Destruction of tunica media with inflammation	+			+	+				
Aortitis									+
Fibrosis		+				+			
Mucopolysaccharide deposition			+						

AV, aortic valve; AW, aortic wall

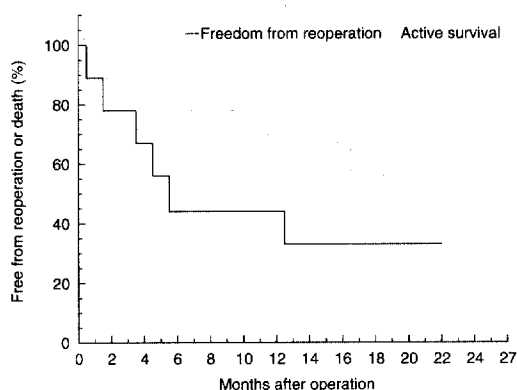


Figure 1. Survival curve and freedom from reoperation curve for postoperative complications in surgical patients with aortic regurgitation caused by Behçet's disease.

(dehiscence of the prosthetic valve with perivalvular leakage, death due to heart failure or infection associated with dehiscence of the prosthetic valve and dehiscence of the sternotomy site). The rate of prosthetic valve detachment was 76 percent (13 of 17 months) (Figure 1). Aortic insufficiency associated with dehiscence of the prosthetic valve developed in 11 of 12 surgical cases (92 percent) with a mechanical valve and 2 of 5 cases (40 percent) with tissue valves (Table 2). The rates of postoperative complication in surgeries with tissue valves were lower than those with mechanical valves ($p=0.053$).

Thirteen of 15 cases (86 percent) were not given immunosuppressive therapy after surgery developed complications. On the other hand, 2 cases which were given postoperative immunosuppressive therapy were free from complications during an average of 19 months (range from 18 months to 20 months). The rates of postoperative complication in cases with immunosuppressive therapy after surgery were lower than those without immunosuppressive therapy after surgery ($p=0.044$).

Four of 9 patients (44 percent) died of heart failure or infection associated with dehiscence of the prosthetic valve and perivalvular leakage within an average 11 of months (range of 2 to 19 months) after surgery (Figure 1).

DISCUSSION

The primary target organs of BD are mucous membranes of the mouth, genitalia and eye. Arterial involvement is not well recognized, but in some cases it may be in the forefront and life threatening¹⁶. Aortic valve involvement occurred late in the course of BD as an arterial lesion of BD that occurred at 3.2 to 7.9 years in the course of BD¹⁷. We observed the mean period of 3 years and 11 months between the first sign of BD and the discovery of aortic valvular lesion. However, most patients (78 percent) experienced abrupt dyspnea on exertion.

The pathogenesis of valvular regurgitation in BD is unknown. The contributive factors were suggested as

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dilatation of the aortic or mitral annulus caused by atypical inflammation, destruction of the valve tissue itself, diffuse aortitis of the ascending aorta and aneurysm of Valsalva sinus^{6, 8, 10}. The microscopic features of the aortic valve in BD have been reported from normal to fibrosis with/without inflammation^{5, 6, 8, 10}. The histologic features of the aortic wall have also been reported as normal, fibrosis or acute aortitis^{5, 6, 10}. The histologic findings of aortitis in BD are well known; the active vasculitis stage is characterized by intense infiltration of inflammatory cells, particularly involving the media and adventitia. They consist predominantly of neutrophils, lymphocytes and plasma cells, mixed with histiocytes and eosinophils and sometimes with giant cells. In the scar stage, fibrous thickening of intima and adventitia were observed, as well as fibrous scar with condensation of elastic lamina in media¹⁸.

In our cases, we observed central perforation of the cusp with Valsalva sinus aneurysm in 4 cases and annulus dilatation in 3 cases among 9 surgical cases. The pathologic finding of the aortic valve was nonspecific and the diffuse myxoid degenerative change was common (75 percent). Aortic wall exhibited evidence of medial destruction with nonspecific inflammation to active aortitis. Therefore, we speculated that aortic insufficiency in BD might be associated with myxoid degeneration of the aortic valve, annular ectasia, aneurysm of Valsalva sinus with nonspecific inflammation or with vasculitis of the aortic wall.

BD infrequently requires intestinal or vascular surgical procedures. The recurrence rates were reported as 40 to 55 percent in aortic valve surgery 40 to 80 percent in intestinal surgery and 74 percent in arterial surgery^{12, 13, 17, 18}. Ando et al.¹³ showed that the rates of mortality and prosthetic valve detachment were 20 percent and 40 percent after surgical treatment of the 10 patients with BD involving aortic regurgitation in comparison with 44 percent and 67 percent in our study (Figure 1). But they used postoperative steroid in all patients. The recurrence of intestinal ulceration, arterial aneurysm, graft thrombosis and prosthetic valve detachment developed in situ or in a nearby operation site. Le Thi Huong¹⁷ suggested that the high recurrent rate of aneurysm or graft thrombosis was developed at the anastomosis site with synthetic prosthetic prosthesis or venous graft in the arterial lesion with BD. The pathogenesis for the high rate of tissue destruction at the operation site is unknown. Le Thi Huong, however, suggested that it was "arterial wall aphthae" resulting from pathergy pheno-

menon, indicating that the aneurysmal wall of the artery has severe medial necrosis resembling epidermal and dermal junction necrosis in the mucocutaneous lesions^{17, 19}. He also suggested that the efficacy of corticosteroid and/or immunosuppressive drug might reduce inflammation.

In our study, 13 of 17 surgeries resulted in inflammation at the detached prosthetic valve and fragile lesions at the suture site. One case showed poor tissue healing at the sternotomy site. We observed a similar phenomenon to pathergy with pustules or a sterile abscess-like lesion at the suture site or incision site. These also showed detachment of the prosthetic valve with perivascular leakage and inflammation at the suture site. We could not, however, document the medial necrosis of the aortic wall in 2 surgical cases.

Intensive anti-inflammatory therapy might reduce the inflammatory reaction on the anastomotic site of the aortic wall and reduce complications, such as dehiscence of the prosthetic valve or sternotomy wound. Several authors^{12, 13, 17, 19} have reported that corticosteroids and/or immunosuppressive therapy were effective in reducing inflammation. Therefore, we initiated immunosuppressive therapy with prednisolone 1 mg/kg and azathioprine 100 mg daily in 2 cases. These 2 cases have not shown complications after aortic valve replacement. In contrast, 13 of 15 surgical cases (87 percent) which were not given postoperative immunosuppressive therapy showed several complications, such as dehiscence of the prosthetic valve and perivalvular leakage.

Two kinds of aortic valve, including mechanical valve, bovine or autologous tissue valve (pulmonic valve, pericardium), were used. Eleven of 12 cases with mechanical valves and 2 of 5 cases with tissue valve developed postoperative complications. The recurrence rate was higher in the mechanical valves (92 percent) than tissue valves (40 percent). Even though the differences between mechanical and tissue valves were not statistically significant because of low parameter, it could be considered as one of the factors associated with postoperative complication.

Poor prognostic factors in BD include male gender and a young age of onset, involvement of CNS and arterial or venous involvement, vein and gastrointestinal perforation¹⁷. In addition, we suggest including aortic valve involvement as a poor prognostic factor because of the high mortality rate (44 percent) in our cases.

In summary, perforation of the valve cusp, aneurysm of Valsalva sinus and diffuse myxoid degeneration of the valve were common pathologic findings. Valve replace-

ment with tissue valves and intensive postoperative immunosuppressive therapy may be important factors for postoperative complications. But further studies are needed to get clinical significance.

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